Mapping of Oxygen By Imaging Lipids relaxation Enhancement (MOBILE) in experimental tumor models: comparison with R2*, R1 H2O, and OxyLite fiber optic probes.

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Purpose and objectives: Tumor hypoxia is acknowledged as a major factor of resistance of solid tumors to treatment. Improving tumor oxygenation at the time of treatment could lead to an improved response to therapy (1). In order to individualize the treatments and select patients who could benefit from tumor reoxygenation, there is a critical need for methods able to monitor dynamically and noninvasively tumor oxygenation. Variations in T_1 and T_2* are potentially valuable MRI tools to changes in tumor oxygenation. T_2* is sensitive to the relative Hb/HbO2 ratio in vessels (2), while T_1 change is sensitive to dissolved oxygen which acts as a T_1-shortening paramagnetic contrast agent (3). The purpose of the current work was to compare the MOBILE technique, a method developed to map variations in oxygenation based on the changes in the relaxation properties of the tissue lipids by exploiting the higher solubility property of oxygen in lipids than in water (4), with R_2*, R_1 H_2O, and simultaneous quantitative oxygen measurements using fluorescence quenching fiber optic probes. Changes in tumor oxygenation were induced by an hyperoxic breathing challenge in order to determine correlations between the response assessed using each technique vs the OxyLite™ technique.

Material and Methods:

Tumor models & protocol: Mammary tumor models (NT-2 and Human MDA-MB-231 cells) were implanted orthoptically in FBV and FVB/N mice, respectively (n=5/model). Mice were anesthetized using isoflurane and the MR compatible OxyLite probe was inserted into the tumor. Three MR measurements of each type (R_1 H_20, R_1 Lipids, R_2*) were acquired during air breathing and repeated during carbogen breathing.

MR experiments: Experiments were performed with a 11.7T (Bruker, Biospec), and with a quadrature volume coil (inner diameter of 40 mm). A segmented IR FISP (Inversion-Recovery Fast Imaging with Steady state Precession) sequence (SSFP FID mode) was used to acquire parametric images of T_1 relaxation time. The acquisition parameters were TR/TE/FA/BW/matrix = 4 ms/1.2ms/5°/100kHz/64x64, 4 segments, and a total acquisition time of 1min20s. For the lipids experiment, we first evaluated the difference in Hertz between water and lipid peaks on a single pulse spectrum. These offsets were then used as an imaging frequency offset in the same IR FISP protocol and the water signal was spoiled. Images were treated using Matlab to determine the T_1 relaxation. For T_2* measurements, a Multi Gradient Echop (MGE) sequence is performed with 8 echoes (between 3.5 ms & 31.5ms) with a total acq. time of 4min 48s. A 256x256 matrix is obtained with TR/flip angle/slice thickness=1500ms/30°/1mm.

Results:

Tumor oxygenation was increased in the majority of the tumors (7/8) under carbogen breathing conditions, as shown using the OxyLite probe. Mean relative changes in relaxation rates with respect to the hyperoxic challenge were compared between R_1 H_20, R_1 Lipids, and R_2*, with relative changes of 2.1 +/- 1.0% (ΔR_1 H_20), 10.1 +/- 4.8 % (ΔR_1 Lipids), and 9.8 +/- 4.6 % (ΔR_2*) (Fig.1). In addition, the tip of the OxyLite™ probe could be localized on the MR images, allowing the comparison of the quantitative values obtained by fluorescence quenching and the MR relaxation values obtained in the sensitive region of the probe (3*3 pixels with the exclusion of the central pixel). The best correlation was found between ΔR_1 Lipids and ΔpO_2, presenting a positive linear fit with a slope of 0.0027 ± 0.0023 (r^2=0.22) (Fig.2). Indeed, ΔR_1 H_20 presented a negative slope vs ΔpO_2 (-0.0012 ± 0.0006; r^2=0.37) (Fig.3), and ΔR_2* presented a positive slope (0.4527 ± 0.4120; r2=0.17) (Fig.4), while expected to be negative. Typical maps of the relative difference in relaxation rates before and during the carbogen challenge were generated in order to compare the sensitivity of the R_1 of lipids (MOBILE), R_1 of H_20, and R_2* methods (Fig.2,3,4, bottoms).

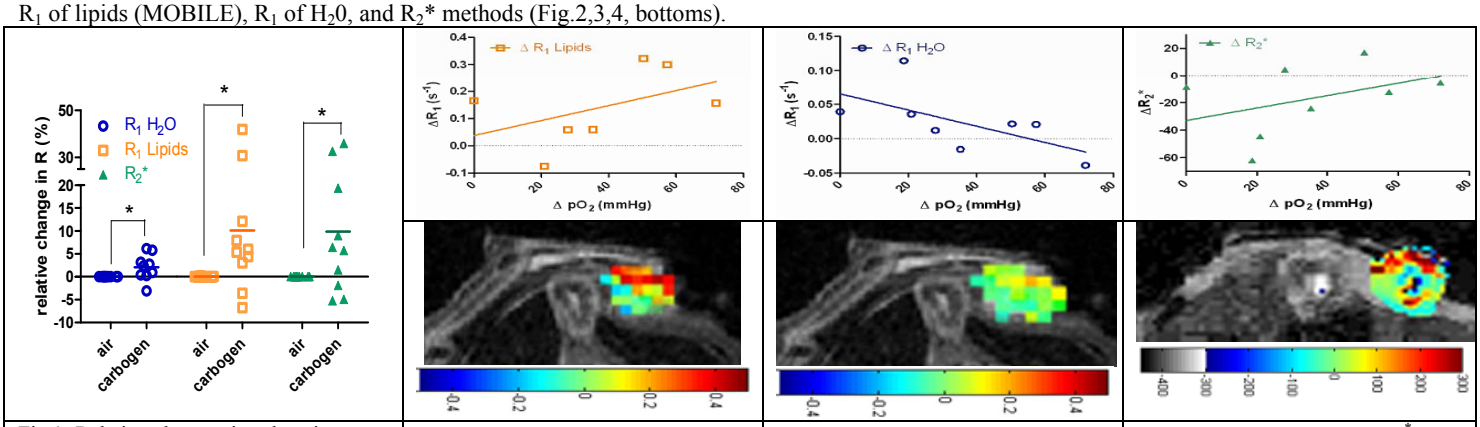

Fig.1. Relative changes in relaxation rates with respect to carbogen breathing.

Fig.2. Relation between ΔR_1 Lipids and ΔpO_2 + typical map of change in R_1 Lipids during carbogen breathing

Fig.3. Relation between ΔR_1 H_2O and ΔpO_2 + typical map of change in R_1 H_2O during carbogen breathing

Fig.4. Relation between ΔR_2* H_2O and ΔpO_2 + typical map of change in R_2* during carbogen breathing

Conclusions:

MOBILE offers an increased sensitivity when monitoring changes in tumor oxygenation compared to R_1 of water or R_2*. However, it is important to keep in mind that oxygen is not measured in the same compartments with R_1 or R_2* (i.e. R_1 is assessing tissue pO_2 whereas R_2* is assessing pO_2 in the vascular compartement). The information afforded by both techniques might be complementary. MOBILE could therefore be a useful complementary tool to R_2* to dynamically assess changes in tumor oxygenation quantitatively.

References:

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